as bacteria) that metabolize oxygen, contain the enzyme superoxide dismutase, which rapidly converts superoxide anion to less toxic products. Some enzyme systems producing superoxide anion are dependent on the partial pressure of oxygen and, therefore, this mechanism could be toxic at higher P_{O_2}. Animals that became less sensitive to oxygen toxicity by previous exposure to 85 percent oxygen at 1.0 atm have increased activity of superoxide dismutase.[63] Superoxide anion may not only be involved in many inflammatory processes but it may also be important in protecting tissues against injury.

Another possible defense mechanism against oxidants exists in the erythrocyte and is dependent upon the presence of the hexose monophosphate-shunt and the reduction of glutathione. Hexose monophosphate-shunt may be important in the lung by providing nicotinamide adenine dinucleotide phosphate (NADPH), which may be used either to reduce glutathione and protect from other oxidants or to resynthesize injured cellular components.[56,64,65]

Recently, Dr. Abe and I[66] have been studying lipid metabolism in lungs of rats recovering from three days of exposure to 100 percent oxygen. Immediately after exposure to oxygen there is a relatively small increase in saturated phosphatidylcholine. However, after recovering in air for two to four days, the saturated phosphatidylcholine almost doubles in content and there are also pronounced increases in the incorporation of precursors, such as palmitate, glycerol and lysophosphatidylcholine, into the saturated phosphatidylcholine of lung slices. Furthermore, if the animals are given large doses of hydrocortisone, approximately 15 mg per kg of body weight every 12 hours, the saturated phosphatidylcholine is about 30 percent more than in lungs of rats exposed to oxygen but given 0.9 percent sodium chloride solution instead of hydrocortisone.

The type II epithelial cells, which increase after oxygen toxicity, contain large quantities of saturated phosphatidylcholine as a component of the pulmonary surfactant. Therefore, our findings are consistent with the evidence that the type II epithelial cells proliferate after injury from oxygen and that this proliferation may be increased by giving hydrocortisone. We also confirmed findings in earlier studies by Sahebjami, Gacad and Massaro[67] who found that hydrocortisone leads to a more rapid decrease of lung weight after oxygen toxicity than if the animals were given a control injection of 0.9 percent sodium chloride solution. Furthermore, the content of DNA did not increase significantly in lungs of animals receiving hydrocortisone, whereas it did increase in the control animals. The interpretation of the DNA data is perhaps related to a decrease of the content of inflammatory cells of the lung when hydrocortisone is given, but one might also expect more DNA as the type II cells proliferate.

Therapy of ARDS: Positive End-Expiratory Pressure

DANIEL H. SIMMONS, MD, PhD

I SHOULD LIKE to present some therapeutic measures that have received some degree of acceptance for ARDS. As I shall discuss in detail the usefulness of a relatively new modality of therapy, maintenance of increased lung volumes by continuous positive end-expiratory pressure (PEEP), I will mention other modalities only briefly.

Since life-threatening hypoxemia is the most outstanding manifestation of ARDS, high inspired concentrations of oxygen should be beneficial. Although this is often helpful in mild cases, it may not adequately oxygenate arterial blood in severe ones and, as previously reported by Drs. Nash and Tierney, may in itself lead to worsening of the condition.

Fluid management is critical in therapy of ARDS. Fluid administration to increase blood volume is occasionally necessary to avoid hypoperfusion caused by decreased cardiac output, especially during PEEP. However, treatment of ARDS usually requires the contrary procedure—fluid restriction or diuresis, or both—to decrease small vessel pressure and lung water content and to reverse the basic abnormality, as discussed by Dr. Brigham. The value of infusing colloid-containing solutions to decrease the pulmonary edema or to treat hypoperfusion is questionable; it probably leads to an increase in lung water and worsening of the condition as much as does administration of crystalloid solutions.

Heparin was originally used because platelet thrombi were found in the lungs of many patients. However, this modality remains controversial; there is little substantial evidence that it reduces morbidity or mortality.

The use of steroids to prevent inflammatory changes in the alveolar wall is also controversial.

There is no substantial evidence that these drugs reduce morbidity or mortality, despite indirect evidence from animal experiments—as discussed previously by Dr. Tierney—that they might be beneficial.

Extracorporeal membrane oxygenation (ECMO) has been tried as a temporary means of maintaining tissue oxygenation. It might be used when lung gas exchange for oxygen has deteriorated to the point where it can no longer maintain life or when dangerously high concentrations of oxygen must be administered for prolonged periods. Extracorporeal membrane oxygenation is at present in the experimental stage.

Maintaining alveoli and airways patent by continuously or periodically increasing lung volume has been accepted as a major advance in the therapy of ARDS; it has been shown to improve both inadequate arterial oxygenation and low lung compliance, two of the major physiologic defects. However, the critical question of whether these maneuvers improve oxygenation of tissues has not been established, because concomitant worsening of tissue perfusion may negate the potential benefit of improving arterial oxygenation.

Therapy aimed at improving patency of alveoli and airways has included use of large tidal volumes (when the patient is on a mechanical ventilator), periodic hyperinflation (during either spontaneous breathing or mechanical ventilation), and the usual methods for clearing of airway secretions.

The most extensive advance in the treatment of ARDS is maintenance of continuously increased lung volumes by PEEP. Despite dramatic improvements in arterial oxygenation[68-78] and related lung compliance,[70,73] we do not have definite evidence that PEEP is of value in all patients or even that it is not detrimental in many others.

Positive end-expiratory pressure has been used most often with mechanical ventilation, as first suggested by Petty and Ashbaugh in 1971.[4] Continuous positive airway pressure (CPAP) during spontaneous breathing, first recommended by Gregory and associates[74] for use in the infant respiratory distress syndrome, has also been used recently in the adult syndrome.[71-73,75] And even more recently, the combination of PEEP and CPAP, with intermittent mandatory ventilation (IMV) and a combination of spontaneous breathing and mechanical ventilation, has been suggested to avoid different adverse effects of both PEEP and CPAP.[76]

In many but not all studies, a major complication of PEEP has been a decrease in cardiac output and oxygen delivery with potentially worsened tissue oxygenation, despite its beneficial effect on arterial oxygenation.[1,68,72] This complication might be avoided by use of CPAP during spontaneous breathing,[71,72,75] although hemodynamic effects of CPAP have not been systematically studied in ARDS.[77] On the other hand, CPAP results in adverse and potentially serious ventilatory responses.[76,78,79] However, this has not been well documented; the thorough review of CPAP by Downes[72] does not even include this potential complication.

Therefore, Dr. Gothe and I did a systematic study of hemodynamic and respiratory responses of a model of ARDS induced by intravenous infusion of oleic acid into anesthetized dogs.[73,80] Eight of these dogs were subjected to various end-expiratory pressures during mechanical ventilation (PEEP) and six to the same levels of end-expiratory pressure during spontaneous breathing (CPAP).

There were several objectives: The first was to determine and compare both hemodynamic and ventilatory responses with the two types of increased end-expiratory pressure. The second was to determine whether there was improved tissue oxygenation with either technique, as shown by changes in the oxygen tension of mixed venous blood (P_{VO_2}), an indicator of the state of tissue oxygenation.[81] The third objective was to determine whether pulmonary reflexes, arising in the lung, played a role in the ventilatory responses to CPAP and if they had an adverse effect on ventilation.

This study was designed to avoid the following problems associated with most reports about the use of PEEP and CPAP: (1) In many studies, P_{aO_2} was adequate, if not normal, before administration of PEEP, which would therefore not be clinically necessary. Under these conditions, the only possible important effect is a decrease in cardiac output and oxygen delivery because of only minor potential for improvement in arterial oxygen content. (2) In most studies, the state of tissue oxygenation was not assessed by criteria such as P_{VO_2}. Although oxygen delivery was often reported, it has not been an adequate criterion for estimating the state of tissue oxygenation; it does not correlate well either with changes in tissue P_{O_2} or development of lactic acidosis. (3) Several studies were done on patients without ARDS but with other diseases, such as chronic obstructive pulmonary disease (COPD) or congestive heart failure.

(4) Many studies were conducted with levels of PEEP inadequate to produce significant changes in severe ARDS. (5) Although findings in some studies showed effects on Pvo_2, the changes were of questionable statistical significance.

In this study, while the dogs breathed 100 percent oxygen, sufficient oleic acid and intravenous fluids were given so that Pao_2 was less than 60 mm of mercury, a condition in which some type of PEEP is thought to be necessary. Measurements were made without any end-expiratory pressure (0 PEEP) and at end-expiratory pressures of 5, 10, 15, 20 cm of water. The means and standard errors of Pao_2 at the various end-expiratory pressures (Figure 11A) confirm that increasing levels of end-expiratory pressure progressively improve arterial oxygenation. The effects of PEEP and CPAP, although statistically different at some levels, would not be significantly different therapeutically.

Figure 11B shows that improvement in arterial oxygenation is due principally to a decrease in

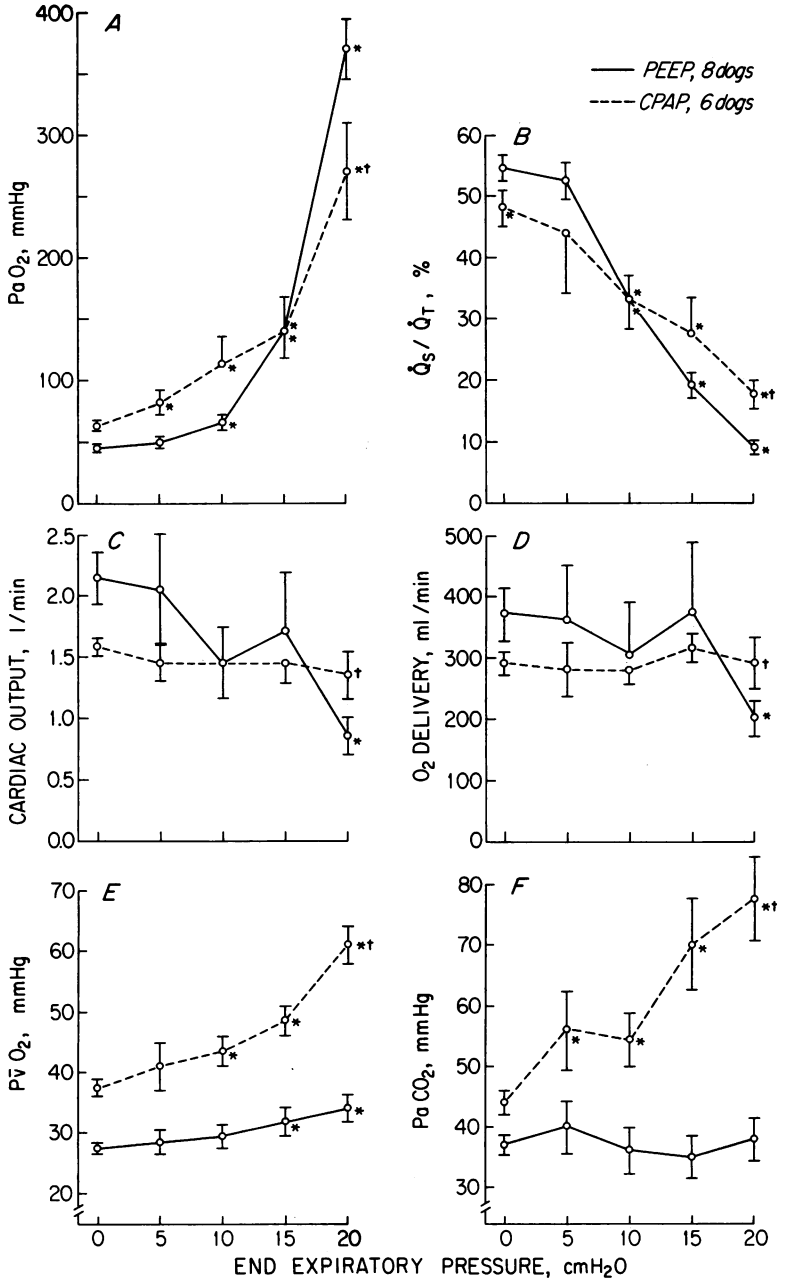

Figure 11.—Mean and standard error at 0, 5, 10, 15 and 20 cm of water of positive end-expiratory pressure (PEEP) during mechanical ventilation (solid lines) and the same levels of continuous positive airway pressure (CPAP) during spontaneous breathing (dashed lines).

* = significant differences from values at 0 cm of water.
† = significant differences between means for PEEP and CPAP at 20 cm of water. See text for detailed discussion.

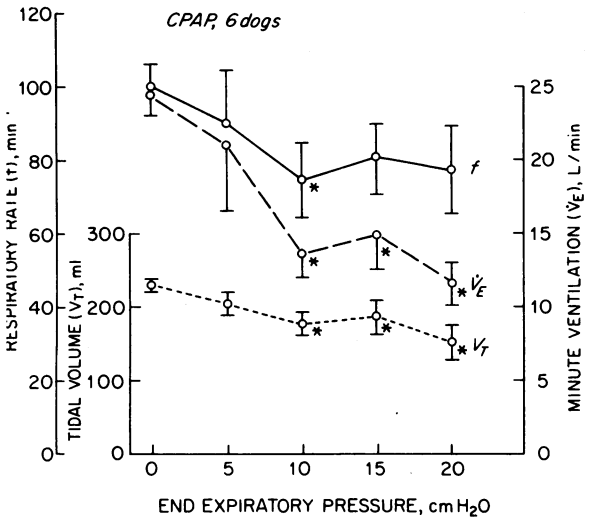

Figure 12.—Mean and standard error of respiratory rate (f), tidal volume (V_T) and minute ventilation (V_E) at 0, 5, 10, 15 and 20 cm of water of CPAP during spontaneous breathing (significant changes as in Figure 11).

intrapulmonary shunts (that is, a decrease in the fraction of total cardiac output, $\dot{Q}_s/\dot{Q}_t$, passing through the lungs without gas exchange for oxygen). There are minor differences between the effects of PEEP and CPAP.

Figure 11C shows a significant fall in cardiac output at the highest levels of PEEP, a complication frequently reported. In contrast to PEEP, there was no significant change in cardiac output during increments of CPAP, resulting in a significantly higher cardiac output at the highest end-expiratory pressure than during PEEP. This difference is probably because mean airway pressure in spontaneously breathing subjects is lower than during mechanical or positive pressure ventilation. This occurs even at the same end-expiratory pressure,[75] resulting in difference in mean intrathoracic pressure, venous return, and cardiac output.

Figure 11D shows essentially the same effects on oxygen delivery, which depends on both cardiac output and arterial oxygen content. Decreased cardiac output seems to have had more effect than improved arterial oxygen content during PEEP.

Figure 11E shows mean P_{VO_2} at various levels of end-expiratory pressure. Two critical points are noted. First, mixed venous oxygen tension rose with increasing end-expiratory pressure during both PEEP and CPAP, suggesting that both maneuvers improved tissue oxygenation,[81] a point not well-established previously. During PEEP, the mean control value of 27.5, approaching the level critical in development of anaerobiasis and lactic acidosis,[82,83] rose to a mean of 34, significantly above the original level. The second important point is that the increase in P_{VO_2} during CPAP was even greater, since arterial oxygenation improved without a decrease in cardiac output. Thus CPAP, when applicable, results in greater improvement in tissue oxygen tensions than does PEEP at the same end-expiratory pressure. One implication of this is that during CPAP lower concentrations of oxygen or less pressure may be necessary than during PEEP.

Because of the difference in hemodynamic responses, CPAP might be preferable to PEEP. However, significant differences in ventilatory responses were also noted. Figure 11F shows that mean arterial carbon dioxide pressure (P_{ACO_2}) remained constant during PEEP with constant mechanical ventilation, as expected. However, P_{ACO_2} rose during CPAP at every level of increased end-expiratory pressure, presumably because of the external ventilatory load, which can decrease ventilation and cause hypercapnea. The increased work of breathing could be both inspiratory and expiratory, as expiration is often active rather than passive during CPAP. Furthermore, the increase in lung volume associated with increased expiratory pressure may result in decreased compliance and increased inspiratory work of breathing. Therefore, although CPAP seems to be preferable to PEEP because of a significant difference in hemodynamic responses, ventilatory responses are a potential drawback.

To examine further the mechanism of the ventilatory response during CPAP, we studied effects of 15 cm of water of CPAP on respiratory frequency (f), tidal volume (V_T) and minute ventilation (V_E) of six dogs (Figure 12). Respiratory frequency was extremely high at the onset; it dropped during CPAP, but not significantly. Tidal volume decreased slightly. The minute ventilation (the product of frequency and tidal volume) fell significantly during CPAP, accounting for the increase in P_{ACO_2}.

In order to block afferent impulses of pulmonary reflexes (which might affect ventilation), these measurements were done before and after cooling the cervical vagi to 2°C. Figure 13 shows that blocking the vagus resulted in a change in breathing pattern from rapid shallow breathing to slow deep breathing. This was probably caused by blocking afferent impulses from stretch recep-

tors in the lung,[84] which may be abnormally active in abnormal situations such as this model of ARDS. Total $\dot{V}_E$ also decreased. However, Figure 14 shows that vagal cooling resulted in a very significant decrease in $PaCO_2$ during CPAP. This can be attributed to the decrease in f, so that the V_T, no longer limited by high flow rates, increases.[84] Despite a decrease in total minute ventilation, $PaCO_2$ improved, indicating that a decrease in dead space ventilation with lowering of f was a major factor.

These data from animal studies suggest that (1) PEEP and CPAP can improve tissue oxygenation when used under appropriate circumstances, (2) CPAP is potentially the more effective of the two at any given level of end-expiratory pressure and (3) CPAP can also cause stimulation of lung reflexes, an abnormal breathing pattern and significant hypercapnea. Perhaps these data will have some significant implications for therapy of ARDS in humans.

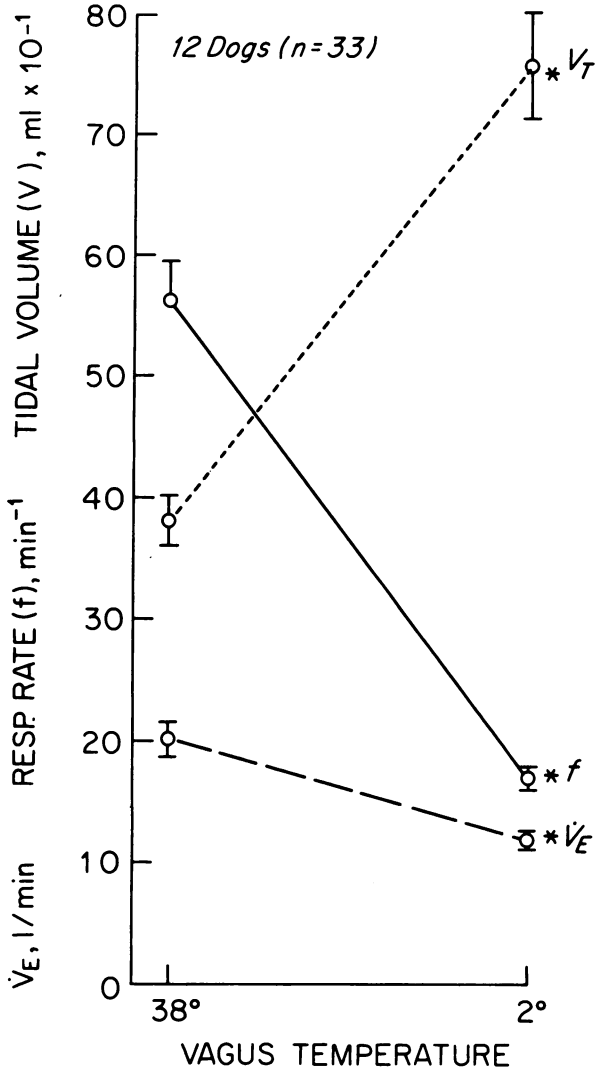

Figure 13.—Mean respiratory rates (f), tidal volumes (V_T) and minute ventilations (V_E) (±SEM) of spontaneously breathing dogs on 15 cm of water of CPAP before and after cooling both cervical vagi to block afferent limbs of pulmonary reflexes.

* = significant changes.

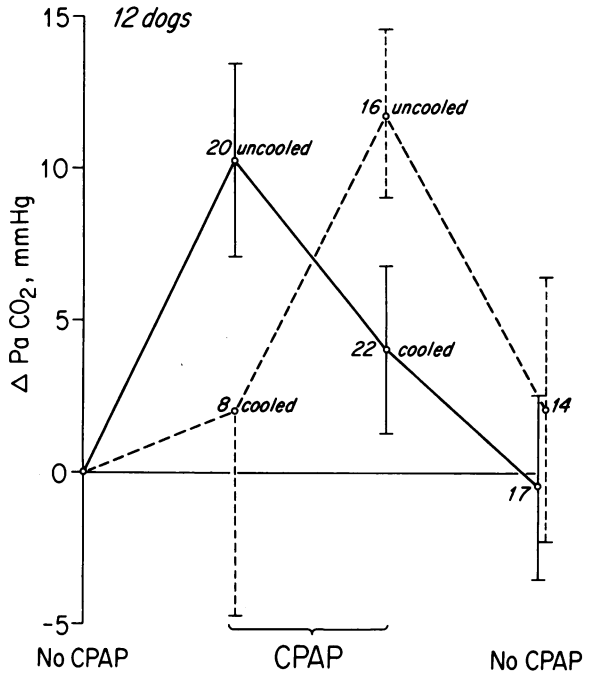

Figure 14.—Mean changes in $PaCO_2$ (±SEM) of 12 spontaneously breathing dogs with and without 15 cm of water of CPAP, and with and without cervical vagal cold blockade (cooled versus uncooled). The order of normal and vagal blockade was alternated in two groups. The number of measurements for each mean is shown.

REFERENCES

1. Hopewell PC, Murray JF: The adult respiratory distress syndrome. Ann Rev Med 27:343-356, 1976
2. Petty TL Newman JH: Adult respiratory distress syndrome (Medical Progress). West J Med 128:399-407, May 1978
3. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. Lancet 2:319-323, Aug 1967
4. Petty TL, Ashbaugh DG: The adult respiratory distress syndrome—Clinical features, factors influencing prognosis and principles of management. Chest 60:233-239, Sep 1971
5. Petty TL: The adult respiratory distress syndrome (confessions of a "lumper") (Editorial). Am Rev Respir Dis 111:713-715, Jun 1975
6. Murray JF: The adult respiratory distress syndrome (may it rest in peace) (Editorial). Am Res Respir Dis 111:716-718, Jun 1975
7. Robin ED, Cross CE, Zelis R: Pulmonary edema. N Engl J Med 288:239-246, 292-304, Feb 1, Feb 8, 1973
8. Katz S, Aberman A, Frand UI, et al: Heroin pulmonary edema—Evidence for increased capillary permeability. Am Rev Respir Dis 106:472-474, Sep 1972
9. Brigham KL, Woolverton WC, Staub NC: Reversible increase in pulmonary vascular permeability after *Pseudomonas aeruginosa* bacteremia in unanesthetized sheep. Chest 65(Suppl):51S-54S, Apr 1974
10. Lung Problem, National Heart and Lung Institute. Respiratory Diseases: Task Force on Problems, Research Approaches, Needs. Bethesda, Md., DHEW Publication No. (NIH) 73-432, 1972, p 171

11. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368-374, Feb 16, 1967

12. Cederberg A, Hellsten S, Miorner G: Oxygen treatment and hyaline pulmonary membranes in adults. Acta Pathol Microbiol Scand 64:450-458, 1965

13. Fuson RL, Saltzman HA, Smith WW, et al: Clinical hyperbaric oxygenation with severe oxygen toxicity—Report of a case. N Engl J Med 273:415-419, Aug 19, 1965

14. Barter RA, Finlay-Jones LR, Walters MN-I: Pulmonary hyaline membrane: Sites of formation in adult lungs after assisted respiration and inhalation of oxygen. J Pathol Bacteriol 95:481-488, Apr 1968

15. Soloway HB, Castillo Y, Martin AM Jr: Adult hyaline membrane disease—Relationship to oxygen therapy. Ann Surg 168:937-945, Dec 1968

16. Kaplan HP, Robinson FR, Kapanci Y, et al: Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys—I. Clinical and light microscopic studies. Lab Invest 20: 94-100, Jan 1969

17. Kapanci Y, Weibel ER, Kaplan HP, et al: Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys—II. Ultrastructural and morphometric studies. Lab Invest 20: 101-118, Jan 1969

18. Robinson FR, Harper DT Jr, Thomas AA, et al: Proliferative pulmonary lesions in monkeys exposed to high concentrations of oxygen. Aerosp Med 38:481-486, May 1967

19. Robinson FR, Casey HW, Weibel ER: Oxygen toxicity in nonhuman primates. Am J Pathol 76:175-178, Jul 1974

20. Katzenstein AA, Bloor CM, Liebow AA: Diffuse alveolar damage—The role of oxygen, shock and related factors—A review. Am J Pathol 85:210-228, Oct 1976

21. Kistler GS, Caldwell PRB, Weibel ER: Development of fine structural damage to alveolar and capillary lining cells in oxygen-poisoned rat lungs. J Cell Biol 32:605-628, Mar 1967

22. Adamson IYR, Bowden DH, Wyatt JP: Oxygen poisoning in mice—Ultrastructural and surfactant studies during exposure and recovery. Arch Pathol 90:463-472, Nov 1970

23. Bowden DH, Adamson IYR: Reparative changes following pulmonary cell injury—Ultrastructural, cytodynamic, and surfactant studies in mice after oxygen exposure. Arch Pathol 92:279-283, Oct 1971

24. Kapanci Y, Tosco R, Eggermann J, et al: Oxygen pneumonitis in man: Light- and electron-microscopic morphometric studies. Chest 62:162-169, Aug 1972

25. Gould VE, Tosco R, Wheelis RF, et al: Oxygen pneumonitis in man: Ultrastructural observations on the development of alveolar lesions. Lab Invest 26:499-508, May 1972

26. Nash G, Foley FD, Langlinais PC: Pulmonary interstitial edema and hyaline membranes in adult burn patients—Electron microscopic observations. Hum Pathol 5:149-160, Mar 1974

27. Bachofen M, Weibel ER: Basic pattern of tissue repair in human lungs following unspecific injury. Chest 65(Suppl, Part I): 14S-19S, Apr 1974

28. Cottrell TS, Levine OR, Senior RM, et al: Electron microscopic alterations at the alveolar level in pulmonary edema. Circ Res 21:783-797, Dec 1967

29. Szidon JP, Pietra GG, Fishman AP: The alveolar-capillary membrane and pulmonary edema. N Engl J Med 286:1200-1204, Jun 1972

30. Bowden DH, Adamson IYR: Endothelial regeneration as a marker of the differential vascular responses in oxygen-induced pulmonary edema. Lab Invest 30:350-357, Mar 1974

31. Hamman L, Rich AR: Acute diffuse interstitial fibrosis of the lungs. Bull Johns Hopkins Hosp 74:177-212, 1944

32. Hill JD, de Leval MR, Fallat RJ, et al: Acute respiratory insufficiency: Treatment with prolonged extracorporeal oxygenation. J Thorac Cardiovasc Surg 64:551-562, Oct 1972

33. Lamy M, Fallat RJ, Koeniger E, et al: Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. Am Rev Respir Dis 114:267-284, Aug 1976

34. Koeniger EL: Survivors of shock-lung syndrome—Pathologic findings in open lung biopsies (Abstract). Lab Invest 36:360-361, Mar 1977

35. Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649-657, Jul 1959

36. Erdmann AJ III, Vaughan TR, Brigham KL, et al: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ Res 37:271-284, Sep 1975

37. Staub NC: Pulmonary edema. Physiol Rev 54:678-811, Jul 1974

38. Brigham KL, Woolverton WC, Blake LH, et al: Increased sheep lung vascular permeabilty caused by Pseudomonas bacteremia. J Clin Invest 54:792-804, Oct 1974

39. Brigham KL, Owen PJ: Mechanism of the serotonin effect on lung transvascular fluid and protein movement in awake sheep. Circ Res 36:761-770, Jun 1975

40. Brigham KL, Owen PJ: Increased sheep lung vascular permeability caused by histamine. Circ Res 37:647-657, Nov 1975

41. Brigham KL, Owen PJ, Bowers RE: Increased permeability of sheep lung vessels to proteins after *Pseudomonas* bacteremia. Microvasc Res 11:415-419, May 1976

42. Blake LH, Staub NC: Pulmonary vascular transport in sheep—A mathematical model. Microvasc Res 12:197-220, Sep 1976

43. Staub N, Nagano H, Pearce ML: Pulmonary edema in dogs, especially the sequence of fluid accumulation in lungs. J Appl Physiol 22:227-240, Feb 1967

44. Taylor AE, Gaar KA Jr: Estimation of equivalent pore radii of pulmonary capillary and alveolar membranes. Am J Physiol 218:1133-1140, Apr 1970

45. Staub NC, Gee M, Vreim C: Mechanism of alveolar flooding in acute pulmonary oedema, *In* Symposium on Lung Liquids, London, 1975—Ciba Foundation Symposium No. 38 (new series). Amsteram, Elsevier, 1976, pp 255-272

46. Brigham KL, Bowers RE, Owen PJ: Effects of antihistamines on the lung vascular response to histamine in unanesthetized sheep: Diphenhydramine prevention of pulmonary edema and increased permeability. J Clin Invest 58:391-398, Aug 1976

47. Foy T, Marion J, Brigham KL, et al: Isoproterenol aminophylline reduce lung capillary filtration during high permeability. J Appl Physiol 46:146-151, Jan 1979

48. Foy T, Marion J, Brigham K, et al: Effects of isoproterenol and aminophylline on sheep lung fluid balance during Pseudomonas induced increased vascular permeability (Abstract). Am Rev Respir Dis 113, No. 4 (part 2 of 2 parts):236, Apr 1976

49. Brigham K, Staub NC: Lung interstitial protein: Studies of lung lymph, *In* Sgouris JT, René A (Eds): Proceedings of the Workshop on Albumin, Feb 12-13, 1975, Bethesda, MD. National Heart and Lung Institute, DHEW (NIH) 76-925, 1976, pp 126-134

50. Harris TR, Rowlett RD, Brigham KL: The identification of pulmonary capillary permeability from multiple-indicator data: Effects of increased capillary pressure and alloxan treatment in the dog. Microvasc Res 12:177-196, Sep 1976

51. Harris TR, Woltz CC, Brigham KL: The inference of pulmonary capillary permeability from lymph and multiple-indicator experiments: Comparison with equivalent pore theory. Proc 29th Ann Conf Engineer Med Biol 18:.228, 1976

52. Harris TR, Brigham KL: The effects of histamine and serotonin on pulmonary lymph and tracer transvascular exchange in awake sheep—Consistency with equivalent pore theory (Abstract). Clin Res 25:37A, Jan 1977

53. Harris T, Brigham K: Permeability effects of histamine and serotonin in the capillary circulation of awake sheep: Comparison of multiple indicator and lymph measurements (Abstract). Am Rev Respir Dis 115, No. 4 (part 2 of 2 parts):336, Apr 1977

54. Brigham K, Snell J, Marshall S, et al: Indicator dilution lung water and vascular permeability in humans: Effects of pulmonary vascular pressure. Circ Res (In press)

55. Marshall S, Brigham K, Snell J, et al: Lung vascular permeability in humans: Correlation with total lung capacity but not with lung vascular pressures (Abstract). Am Rev Respir Dis 115, No. 4 (part 2 of 2 parts):351, Apr 1977

56. Tierney DF, Ayers L, Kasuyama RS: Altered sensitivity to oxygen toxicity. Am Rev Respir Dis 115, No. 6 (part 2 of 2 parts): 59-65, Jun 1977

57. Fisher HK, Clements JA, Wright RR: Enhancement of oxygen toxicity by the herbicide paraquat. Am Rev Respir Dis 107:246-252, Feb 1973

58. Ayers LN, Tierney DF, Imagawa D: Shortened survival of mice with influenza when given oxygen at one atmosphere. Am Rev Respir Dis 107:955-961, Jun 1973

59. Cohen AB, Gold WM: Defense mechanisms of the lung. Annu Rev Physiol 37:325-350, 1975

60. Sackner MA, Landa J, Hirsch J, et al: Pulmonary effects of oxygen breathing—A 6-hour study in normal men. Ann Intern Med 82:40-43, Jan 1975

61. Clark JM, Lambertsen CJ: Pulmonary oxygen toxicity—A review. Pharmacol Rev 23:37-133, Jun 1971

62. Fridovich I: Oxygen radicals, hydrogen peroxide and oxygen toxicity, chap 6, *In* Pryor WA (Ed): Free Radicals in Biology, Vol 1. New York, Academic Press, 1975, pp 239-271

63. Crapo JD, Tierney DF: Superoxide dismutase and pulmonary oxygen toxicity. Am J Physiol 226:1401-1407, Jun 1974

64. Stokinger HE: Pollutant gases, chap 42, *In* Fenn WD, Rahn H (Eds): Handbook of Physiology—Section 3, Vol 2, Respiration. Washington, DC, American Physiological Society, 1965, pp 1067-1086

65. Tierney DF, Ayers L, Herzog S, et al: Pentose pathway and production of reduced nicotinamide adenine dinucleotide phosphate—A mechanism that may protect lungs from oxidants. Am Rev Respir Dis 108:1348-1351, Dec 1973

66. Abe M, Tierney DF: Lipid metabolism of rat lung during recovery from injury (Abstract). Fed Proc 35:479, Mar 1976

67. Sahebjami H, Gacad G, Massaro D: Influence of corticosteroid on recovery from oxygen toxicity. Am Rev Respir Dis 110:566-571, Nov 1974

68. King EG, Jones RL, Patakas DA: Evaluation of positive end-expiratory pressure therapy in the adult respiratory distress syndrome. Canad Anesth Soc J 20:546-558, Jul 1973

69. Nicotra MB, Stevens PM, Viroslav J, et al: Physiologic evaluation of positive end expiratory pressure ventilation. Chest 64:10-15, Jul 1973

70. Suter PM, Fairley HB, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284-289, Feb 6, 1975

71. Greenbaum DM, Millen JE, Eross B, et al: Continuous positive airway pressure without tracheal intubation in spontaneously breathing patients. Chest 69:615-620, May 1976

72. Downes JJ: CPAP and PEEP—A perspective (Editorial). Anesthesiology 44:1-5, Jan 1976

73. Uzawa T, Ashbaugh DG: Continuous positive-pressure breathing in acute hemorrhagic pulmonary edema. J Appl Physiol 26:427-432, Apr 1969

74. Gregory GA, Kitterman JA, Phibbs RH, et al: Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333-1340, Jun 17, 1971

75. Civetta JM, Brons R, Gabel JC: A simple and effective method of employing spontaneous positive-pressure ventilation—Illustrative case reports. Thorac Cardiovasc Surg 63:312-317, Feb 1972

76. Kirby RR, Perry JC, Calderwood HW, et al: Cardiorespiratory effects of high positive end-respiratory pressure. Anesthesiology 43:533-539, Nov 1975

77. Taylor GT, Brenner W, Summer WR: Severe viral pneumonia in young adults—Therapy with continuous positive airway pressure. Chest 69:722-728, Jun 1976

78. Aune H, Stovner J: Respiratory failure in children treated with continuous positive airway pressure. Tidsskr Nor Laegeforen 94:1445-1447, 1974 (In Norwegian)

79. Garg GP, Hill GE: The use of spontaneous continuous positive airway pressure (CPAP) for reduction of intrapulmonary shunting in adults with acute respiratory failure. Canad Anaesth Soc J 22:284-290, May 1975

80. Parker FB Jr, Wax SD, Kusajimi K, et al: Hemodynamic and pathological findings in experimental fat embolism. Arch Surg 108:70-74, Jan 1974

81. Tenney SM: A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. Respir Physiol 20:283-296, Jun 1974

82. Simmons DH, Alpas AP, Tashkin DP, et al: Hyperlactatemia due to arterial hypoxemia or reduced cardiac output, or both. J Appl Physiol 45:195-202, Aug 1978

83. Kasnitz P, Druger GL, Yorra F, et al: Mixed venous oxygen tension and hyperlactatemia—Survival in severe cardiopulmonary disease. JAMA 236:570-574, Aug 9, 1976

84. Davis HL, Fowler WS, Lambert EH: Effect of volume and rate of inflation and deflation on transpulmonary pressure and response of pulmonary stretch receptors. Am J Physiol 187:558-566, Dec 1956

Cigarette Smoking and Early Menopause

WE STARTED LOOKING at our data for one reason or another on menopause and at the same time we were looking at our data on smoking. So we looked at the two of them combined and, lo and behold, we found that there is a striking relationship between smoking and age of menopause. A summary of data . . . shows that women who smoke tend to have an earlier menopause, and the more a woman smokes the earlier the menopause. At age 48-49, for example, among 195 never-smokers only 26 percent were postmenopausal at that time; among heavy smokers, almost twice as many, 46 percent, were postmenopausal; at 50-51, 56 percent of never-smokers, 79 percent of heavy smokers were postmenopausal.

—HERSCHEL JICK, MD, *Boston*

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